REMARKS

Claims 36-81 are pending. Applicants have amended Claims 66-73 and Claims 74-81 to requie that the nucleic acids encode fragments of SEQ ID NO: 17, or the complement thereof. Applicants have amended dependent Claims 66 and 74 such that Claims 67-73 and 75-81 properly depend therefrom, respectively. Applicants have added Claims 82-87. The amendments and new claims do not add new matter and are fully supported by the specification as filed. Support for the amendments to Claims 66-73 and 74-81 can be found, for example, at page 4, lines 14-18, at page 7, lines 28-31, and elsewhere throughout the specification. Support for new claims 82-87 can be found, for example, at page 4, lines 14-18, at page 7, lines 28-31, and elsewhere throughout the specification.

On May 16, 2006, the undersigned, Examiner Li and Supervisor Campell conducted a personal interview to discuss the Office Action mailed February 27, 2006. More specifically, during the interview, the restriction requirement, the claim objections, the enablement rejections under 35 U.S.C. § 112, first paragraph, the new matter rejections under 35 U.S.C. § 112, first paragraph, the provisional double patenting rejection, and the rejections under 35 U.S.C. § 103 raised in the Office Action were discussed. The undersigned and the Examiner agreed to the following: (1) Claims 36-38, 42-53, and 57-65 are linking claims and will be examined in the subject application. (2) Claims 66-73 and 74-81 would be amended such that Claims 67-73 and Claims 75-81 properly depend from Claims 66 and 74, respectively, and the objection to the claims would be withdrawn. (3) Applicants agreed to provide a declaration demonstrating that many HCV epitopes of 8 amino acids and longer were known at the time of filing, and the enablement rejection would be removed with respect to claims that reflect this size of antigen. (4) The new matter rejections would be withdrawn in view of Applicants' disclosure. (5). The double patenting rejection would be overcome by submitting a terminal disclaimer. (6) The § 103(a) rejection would be removed in view of the fact that the cited art, Hultgren, Encke and Tam, do not render the claimed invention obvious.

Claims 36-87 are now presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed February 27, 2006. For the reasons set forth below, Applicants respectfully traverse and request notification that the pending claims have been allowed.

Specification

The Examiner has objected to the specification under M.P.E.P. § 608.01 as containing an embedded hyperlink and/or other form of browser-executable code. Applicants have amended the specification to remove the embedded browser-executable code and respectfully request that the Examiner withdraw the objection.

Election/Restriction

The Examiner has noted that in Applicants' Amendment and Response to Restriction Requirement mailed December 15, 2005, Applicants elected invention I, directed to methods for treating an HCV infection. The Examiner states that "Applicants are reminded to amend the claims to the scope of hepatitis C virus for reflecting *[sic]* examination on the merits." *Office Action* at 2. Applicants disagree, and maintain that the Examiner is required to examine the pending claims.

In the Restriction Requirement mailed on November 17, 2005, the Examiner noted that Claims 36-38, 42-53, and 57-65 "are link(s) *[sic]* invention groups I-II and III." Applicants responded to the Restriction Requirement by electing invention I without traverse. *See, Amendment and Response to Restriction Requirement* mailed Dec. 12, 2005. The pending claims are either linking claims (*i.e.*, Claims 36-38, 42-53, and 57-65) or relate to the elected invention (*i.e.*, Claims 39-41, 54-56, and 66-81).

Pursuant to M.P.E.P. § 809,

> The linking claims must be examined with, and thus are considered part of, the invention elected. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked invention must be withdrawn. Any claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability.

Accordingly, an amendment to the claims to limit the scope to HCV is not necessary. This was agreed upon at the on May 16, 2006, and Applicants respectfully request that the Examiner examine all of the presently pending claims.

Claim Objections

The Examiner has objected to Claims 67-73 and 75-81 under 37 C.F.R. § 1.75(c) as allegedly being in improper dependent form for failing to further limit the subject matter of Claims 66 and 74, respectively. Applicants have amended Claims 66 and 74 to recite "wherein said nucleic acid comprises a nucleic acid sequence encoding at least 8 consecutive amino acids of the sequence of SEQ ID NO: 17." Claims 66-73 and 74-81 recite nucleic acid sequences encoding at least 8, 10, 12, 20, 50, 100, 250 or 500 consecutive amino acids of SEQ ID NO:17. Thus, dependent Claims 67-73 and 75-81 further narrow independent Claims 66 and 74. Applicants respectfully request that the Examiner withdraw the claim objections in view of the above amendments.

Rejections Under 35 U.S.C. § 112, first paragraph - Written Description/New Matter

The Examiner has rejected Claims 36-81 as allegedly failing to comply with the written description requirement. According to the Examiner, the rejected claims contain matter which was not described in the specification in such a way as to reasonably convey that Applicants had possession of the claimed invention at the time the application was filed. Specifically, the Examiner states that Claims 36 and 51 include the step of identifying a subject in need of an increased titer of viral antigen-specific IgG antibodies, or an improvement in a T cell response. The Examiner maintains that the specification "does not have any description how each particular immune response is measured or accessed *[sic]* in a subject prior to be *[sic]* selected for using said composition comprising HCV viral antigen and ribavirin." *Office Action* at 4.

As agreed during the interview on May 16, 2006, the rejected claims are supported by the disclosure in the specification, which demonstrates that Applicants were in possession of the claimed invention at the time the application was filed, including the steps of 1) identifying subjects 2) providing an immunogenic composition and 3) measuring, as recited in the claims. *See*, Examiner's Interview Summary. Page 5, lines 15-19 the specification states that "[b]y one approach. . . an animal in need of [a] potent immune response to a hepatitis viral antigen (*e.g.*, an animal at risk or already infected with a hepatitis infection) is identified and said animal is provided an amount of ribavirin and a hepatitis viral antigen (either in a single composition or administered separately) that is effective to enhance an immune response to the hepatitis viral antigen." Likewise, page 9, lines 3-8 of the specification describes the identification of an animal

in need of an enhanced immune response. At page 6, lines 22-30, the specification defines an enhanced immune response as "significant increase in immune-mediated protection against the antigen, as [] demonstrated by an increase in the titer of antibody raised to the antigen and an increase in proliferative T-cell responses." Accordingly, the identification step recited in the rejected claims is fully supported by the specification, as demonstrated by the disclosure found on page 5, lines 15-19, page 9, lines 3-8 and page 6, lines 22-30 of the specification, as well as elsewhere in the specification.

The specification also includes working examples, *i.e.*, EXAMPLES 1-15, describing the execution of each of the steps recited in the claims. EXAMPLE 1 describes the identification of subjects in need of an enhanced immune response. Specifically, EXAMPLE 1 "describes several assays to evaluate the adjuvant activity of ribavirin" (*e.g.*, the ability to enhance an immune response as defined on page 6, lines 22-30) in mice that were immunized with rNS3, thereby describing the "identification" of a subject in need of an enhanced immune response to a viral antigen. *Specification*, p. 11, lines 27-30. Likewise, EXAMPLE 3 describes the identification of a subject in need of an enhanced immune response (*e.g.*, T cell response) to a viral antigen on page 20, lines 11-20. Notably, pages 57-62 include an extensive disclosure regarding diagnostic embodiments to detect HCV, which are useful in identifying individuals in need of en enhanced immune response against HCV antigens (*e.g.*, an animal at risk or already infected with a hepatitis infection, as described at page 5, lines 15-19).

EXAMPLE 1 also describes the step of providing to said subject an immunogenic composition comprising a viral antigen and ribavirin. *Specification*, p. 11, line 30 - page 12, line 2. Antibody production is measured as described on page 12, lines 3-10. Enhanced antibody production and antibody titer are described on page 12, lines 11-16. EXAMPLE 3 also describes the administering a viral antigen and ribavirin to an animal in need thereof, followed by the measurement of the T-cell response to said viral antigen. *Specification,* page 20, lines 11-26.

Accordingly, the disclosure in the instant specification provides several entries that evidence that Applicants were in possession of the claimed invention, including each and every step recited in the claims, *i.e.,* identifying, providing, and measuring, at the time of filing the instant application. Applicants respectfully request that the Examiner withdraw the rejection as agreed upon in the May 16, 2006 personal interview.

Rejection Under 35 U.S.C. § 112, first paragraph - Enablement

The Examiner has rejected Claims 36-39, 42-54, 67-73, and 75-81 as allegedly not being described in the specification in such a way as to enable one skilled in the art to make and use the full scope of the claimed invention. According to the Examiner, the specification is "enabling for inducing an enhanced immune response against an HCV specific antigen NS3/4A encoded by SEQ ID NO: 16 by administering it intramuscularly, [the specification] does not reasonably provide enablement for producing an enhanced specific immune response against a viral antigen with any antigen encoded by an entire HCV genomic sequence or only a fell *[sic]* base pairs of SEQ ISD *[sic]* NO: 16, such as 12 to 20 mers consecutive nucleotides of SEQ ID NO: 16 by any administering methods." *Office Action* at 4.

First, the Examiner argues that

> The specification does not teach which 12 or 20 mers of nucleotides encoding an antigen specific epitope and how to select an epitope along a DNA molecule comprising at least 2061 base pairs set forth in SEQ ID NO: 16. The specification does not provide sufficient evidence or adequate guidance to support the broadly claimed invention. *Id.* at 5.

According to the Examiner, "[t]he level of skill in the art to perform the full scope of invention *[sic]* should be at the PhD level or holding an advanced degree in virology and immunology for selecting a suitable 10 amino acids and test *[sic]* each of the selections for the ability of inducing an enhanced immune response." *Office Action* at 6.

Next, the Examiner asserts that the scope of the claims, which recite "immunogenic compositions comprising a nucleic acid molecule encoding [a] viral antigen" nucleic acids encoding viral antigens," renders them unpatentable under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner correctly points out that

> State of art *[sic]* [] teaches that HCV antigenic polypeptide or polypeptide but not the whole HV genome is able to induce an immune response after administering into an animal. It is unpredictable whether the injection of a whole viral genome or the HCV genome into a subject will induce an enhanced immune response or produce a replicating or infectious hepatitis C viral RNA since transfecting a subgenomic HCV into a cell line can produce infectious HCV RNA in vitro as evidence by Lohman et al. (Science 1999, Vol. 285, pp. 110-113, see abstract) or an acute or persistent infection in vivo as evidenced by Forns et al. (PNAS 2000, Vol. 97, pp. 13318-13323, see abstract. *Id.* at 5-6.

For the reasons set forth below, Applicants maintain that the rejected claims are enabled, as agreed upon during the May 16, 2006 interview.

Applicants first address the Examiner's assertion that the skilled artisan would not be able to determine epitopes along SEQ ID NO:17 given the instant specification. An application enables the claims "if one skilled in the art, after reading the[] disclosure[], could practice the invention claimed ... without undue experimentation." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). Further, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). As discussed below, the skilled artisan, after reading the disclosure could practice the claimed invention without any experimentation.

Numerous viral epitopes (and thus nucleic acid sequences encoding the same) including HCV epitopes were "well known in the art" prior to the effective filing date of the instant application. Applicants submit herewith a Declaration by Matti Sällberg, D.D.S., Ph.D., a co-inventor of the subject application and an expert in the field of virology and immunology. Dr. Sällberg attests to the fact that "[s]everal viral epitopes, in particular, epitopes as small as 8 consecutive amino acids of NS3/4A, were known to those in the field of virology and immunology prior to the filing of the subject application." *Sällberg Decl.*, ¶5. Dr. Sällberg refers to International Patent Application Number WO 95/22317, ("Vitello et al."), which was published long before the priority date of the subject application to support this assertion. Vitello et al. describe several method to identify and optimize several CTL peptides for many different viruses, including HCV. (*See, e.g.*, pages 15-20). Vitello et al. note that CTL-inducing peptides can be between 4 to less than 30 amino acid residues in length. (*See,* p. `5, lines 16-23).

Dr. Sällberg also refers to International Patent Application Number WO 95/12677 ("LeRoux-Roels et al."), also published long before the priority date of the subject application. LeRoux-Roels et al. establishes that no fewer than 25 different 8mer peptides spanning the NS3/4A molecule are immunogenic. (*See,* pp. 23-24). Accordingly several approaches to screen for antigenic peptides at least 8 amino acids in length were known, and in fact at least 25 8mer peptides within NS3 were reported to be antigenic.

The Sällberg declaration along with the supporting evidence in Vitello et al. and LeRoux-Roels et al. clearly demonstrate that the state of the art at the time of the effective filing date of

the instant application was such that the skilled artisan, given Applicants' disclosure could readily practice the now claimed invention without experimentation. Accordingly, Applicants respectfully request that the Examiner withdraw these enablement rejections as agreed upon in the May 16, 2006 interview in view of the above evidence.

Applicants next address the Examiner's assertion that the claims are not enabled because they allegedly encompass the whole HCV genome. Applicants would first like to point out that the rejected claims recite "providing to said subject an *immunogenic composition* comprising a viral antigen and ribavirin." As such, viral antigens that fail to elicit an immune response are not encompassed by the claims. Applicants also wish to emphasize that, based on the understanding in the field, one of skill in the art would readily appreciate that the use of "an entire viral particle or even an entire HCV particle" would be inoperable in an immunogenic composition and, thus, one of skill in the art would not use an entire intact viral particle in an immunogenic composition. M.P.E.P. §2164.08(b) provides:

> The presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *M.P.E.P. §2164.08(b).*

The specification includes considerable data demonstrating that ribavirin is an adjuvant when co-administered with an antigen. *See, e.g.,* Examples 1-15. The determination of whether a particular formulation of ribavirin and viral antigen enhances an immune response is straightforward and routine in the field. It does not require undue experimentation to make and use the claimed compositions. The determination of whether co-administration of a viral antigen and ribavirin enhances an immune response requires only the step of comparing the immune response produced when the formulation includes ribavirin to the immune response produced when the formulation does not contain ribavirin as described in the examples disclosed herein. It does not require undue experimentation to perform these tests. To the contrary, these tests are routinely conducted during the formulation of most immunogenic compositions that contain an adjuvant.

As discussed during the interview on May 16, 2006, and as evidenced by the Sällberg declaration, numerous viral antigens, including HCV viral antigens were known and publicly

available to those skilled in the art at the time of filing of the instant application. In other words, no experimentation is required to determine the claimed viral antigens. Further, regarding the Examiner's second argument concerning the inclusion of embodiments that encompass nucleic acids that are infectious or produce replicating viral particles, Applicants note that it is improper to reject a claim as allegedly being non-enabled because they may encompass inoperable embodiments. Even if this were not the case, Applicants' recitation of the term "immunogenic compositions" in the claims excludes antigens that fail to elicit an immune, contrary to the assertions of the Examiner.

In view of the above, as agreed at the interview of May 16, 2006, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph for lack of enablement.

Double Patenting

The Examiner has provisionally rejected Claims 36-40, 42-55, and 57-65 as being obvious over Claims 34-47, 51-55, 57-70, and 72-80 of co-pending U.S. Patent application No. 10/719,619. Applicants submit herewith a Terminal Disclaimer, thereby addressing and overcoming the Examiner's provisional rejection of the claims. Applicants respectfully request that the Examiner withdraw the provisional double patenting rejection.

Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 36-81 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Encke et al. (*J. Immunol.* 1998, Vol. 161, pp. 4917-4923), Hultgren et al. (*J. Gene. Virol.*, 1998, 79:2381-2391)("Hultgren") and Tam (U.S. Patent No. 5,767,097)("Tam").

The Examiner states that Encke et al. teach that DNA-based immunization of HCV antigens gave detectable antibody responses in subjects but that the authors do not teach the use of ribavirin in combination with the HCV antigens to produce an enhanced immune response.

The Examiner also argues

> Tam R. teaches a method for producing an enhanced immune response, preferentially*[sic]* the TH1 type immune response to a specific antigen by administering a composition comprising a viral component with a non-viral component of ribavirin*[sic]* into patient (Claims 1-9). Tam et al. does not teach to use *[sic]* HCV antigen for the *[sic]* co-administration. *Office Action* at 7.

The Examiner asserts that Hultgren et al. teach a method for inducing an enhanced Th1-type immune response by administering HBV and HCV antigens on the basis of daily administration of ribavirin. The Examiner argues:

> Hultgren et al. teach a method for inducing an enhanced TH-1 type cellular immune response, such as Th1 type of cytokine secretion, such as IL2 or INFγ*[sic]* (Fig. 5) for HBV e Antigen and humoral antibody with HBV e antigen (Fig. 4 and 5) and HCV NS3 or HCV core antigen (Fig. 4) with daily dosages ranged *[sic]* from 0.75-1.5 mg per day after the mice were immunized with said antigens (See Methods of pages 2382-2383). *Office Action* at 8.

Lastly, the Examiner argues that co-administration of the viral antigen and ribavirin, as recited in the rejected claims, is merely "a designed*[sic]* choice since the functions exhibited by the two drugs administrations*[sic]* are same*[sic]*" and thus the claimed invention is obvious absent unexpected results. *Office Action* at 9. Applicants respectfully disagree.

As discussed at length during the interview on May 16, 2006 and as agreed upon by the Examiner, the Examiner's supervisor, and the undersigned, the instant claims are not obvious in view of Encke et al., Hultgren et al. and Tam. Applicants have discovered that ribavirin can be used as an adjuvant (i.e., to enhance an immune response), and the prior art does not teach this discovery.

Although Encke et al. teaches that intramuscular DNA-based immunizations for various HCV antigens produce detectable antibody responses, as the Examiner has recognized, Encke et al. does not teach the use of ribavirin in combination with these antigens. The Examiner first tries to fill this gap with Tam by arguing that Tam teaches administration of ribavirin and a composition comprising a viral component. The Examiner, however, has misinterpreted Tam, which states in Claim 6:

> 6. A method of treating a patient having a disease which includes a viral component and a non-viral component, the non-viral component being characterized by reduced TH1 levels and increased TH2 levels in activated T lymphocytes, comprising administering ribavirin to the patient under a protocol sufficient to promote the TH1 response and suppress the TH2 response in a patient.

The claim recites the treatment of a patient with a viral disease ("having a disease which includes a viral component") by providing ribavirin. In Tam, there is no evidence, indication, suggestion or motivation for administering any composition with an antigen, much less a

composition comprising an antigen and ribavirin. Tam only describes that the daily administration of ribavirin results in immune -modulation.

Furthermore, Tam illustrates how the field teaches away from the claimed invention. Tam states:

> In addition, we have significantly advanced the prior research by demonstrating that ribavirin modulates the cytokine pattern of an immune response at least in part by promoting a Th1 response and suppressing a Th2 response. In hindsight, this discovery is not inconsistent with prior research. First, ribavirin is known to inhibit both functional humoral immune responses, (Peavy et al, 1981, J Immunol 126: 861-864, Powers et al, 1982, Antimicrob Agents Chemother 22: 108-114) and IgE-mediated modulation of mast cell secretion (Marquardt et al, 1987, J Pharmacol Exp Therapeutics 240: 145-149, (both Th2 lymphokine-mediated events). (*See Column 2, lines 65-67 and Column 3, lines 1-9).*

Thus, Tam teaches that ribavirin inhibits immune responses. There is, therefore, no suggestion or motivation to use ribavirin to enhance an immune response to an antigen.

The Examiner has also misinterpreted Hultgren et al. The Examiner refers to Figures 4-5 for the proposition that daily administration of ribavirin followed by periodic administration of an antigen enhances an immune response. In fact, the results of Hultgren are the exact opposite.

Hultgren et al., disclose that daily ribavirin therapy accompanied by an immunization with an antigen and Freund's adjuvant results in a slight shift in IgG subclass distribution, however, no differences were seen in the total IgG levels between the treatment groups. (*See Figure 4 and the discussion on page 2386, first paragraph).* This is **immune-modulation** not an enhanced immune response or adjuvant activity.

Although Hultgren et al. describe the daily administration of ribavirin and periodic immunization with an antigen, their approach was different than Applicants co-administration protocol and the results obtained are significantly different. Applicants observed a rise in antibody titers to the specific antigen when ribavirin was co-administered with an antigen, whereas, Hultgren et al. saw no change in antibody titers, only a shift in IgG subclass distribution.

In fact, Hultgren et al., teach away from co-administration of ribavirin and an antigen to enhance an immune response to the antigen. The authors report, for example, that "[t]he highest dose of daily ribavirin completely prevented anti-HBe seroconversion whereas lower ribavirin

doses reduced antibody titers (Fig. 4c)." (*See page 2387, first paragraph).* The authors also state that "[w]e show that ribavirin treatment causes a transient drop in HCV-specific humoral responses during treatment of patients with chronic HCV infection." (*See page 2388, last two lines and page 2389, first paragraph).* Still further, the authors state that "[r]ecent studies have indeed shown that ribavirin is immune-suppressive *in vitro*" and that "similar effects may well be present *in vivo* during treatment of chronic viral hepatitis." (*See page 2389, second paragraph).* Lastly, the authors report that "[h]igh daily doses of ribavirin (>1mg/day) applied to HBeAg-Tg mice totally inhibited anti-HBe seroconversion, clearly showing the immune-suppressive effects of ribavirin *in vivo*." (*See page 2389, fifth paragraph).*

With regard to the point that co-administration is the same as daily therapy followed by periodic administration of an antigen, Applicants submit that the results are not the same, as exemplified in Hultgren et al. Again, according to Hultgren et al., there was no increase in total antibody titer specific for the antigen when ribavirin was given daily and the antigen was administered periodically, whereas by Applicants co-administration protocol a rise in antibody titer was observed.

In contrast to the findings provided by Hultgren et al., Applicant's specification shows that when antigen and ribavirin are co-administered an enhanced immune response is obtained. (*See Figures 1, 2, and Table 1*). Figure 1, for example, shows that 10μg of antigen co-administered with 1 mg of ribavirin generates nearly the same mean antibody titer against the antigen as an immunization with 100 μg of antigen without co-administration of ribavirin. Figure 2 shows that wide ranges of ribavirin, when co-administered with antigen, produce this adjuvant effect. Table 1 shows that by adding ribavirin to a sub-optimal vaccine dose, a commercially available preparation, antigen-specific antibodies became detectable, however, in the absence of ribavirin, no detectable antibodies were observed. Clearly, the enhanced immune response obtained from co-administration of ribavirin and an antigen is significantly different and unexpected from the immune-modulation obtained from daily ribavirin therapy and periodic administration of an antigen. Furthermore, Applicants state:

> As shown in Table 8, the addition of ribavirin to the immunogen prior to the injection does not change the IgG subclass response in the NS3-specific immune response. Thus, the adjuvant effect of a vaccine composition comprising ribavirin and an antigen cannot be explained by a shift in the TH1/TH2-balance. It appears

that another mechanism may be responsible for the adjuvant effect of ribavirin. (*See* page 19, lines 5-10).

In contrast to the Examiner's assertion, the data support the conclusion that co-administration is **not** the same as daily therapy followed by periodic administration of an antigen. Co-administration of ribavirin and an antigen enhances an immune response; whereas, daily ribavirin therapy followed by periodic immunization with an antigen promotes immune-modulation. When ribavirin is co-administered with an antigen it produces an adjuvant effect but when it is provided as a daily therapy and an antigen is periodically administered a shift in IgG subclass is observed but an increase in total antibody titer specific for the antigen is not obtained.

In sum, Enke et al. teach that DNA-based vaccination can be performed with various HCV constructs but there is no evidence or suggestion to co-administer these nucleic acid antigens with ribavirin. Tam teaches that daily ribavirin therapy produces immune-modulation but there is no evidence or suggestion to combine ribavirin therapy with immunization of an antigen to increase the immune response. Hultgren et al. describe daily ribavirin therapy with periodic administration of an antigen. There is no evidence or suggestion in this reference that the ribavirin and antigen are co-administered and daily administration of ribavirin followed by periodic immunization produces immune-modulation not an enhanced immune response. The results Applicant obtained are unexpected because an increase in total antibody titer specific for the antigen was observed when ribavirin and an antigen were co-administered; whereas, the daily ribavirin and periodic introduction of antigen-type protocol, as exemplified in Hultgren et al., did not produce an increase in total antibody titer specific for the antigen (*see Figure 4c in Hultgren et al.)* but rather produced a shift in IgG subclass (i.e., immune-modulation).

In view of the above, Applicants respectfully request that the Examiner withdraw the rejection of Claims 36-81 as agreed upon during the May 16, 2006 interview.

CONCLUSION

The undersigned has made a good-faith effort to respond to the Office Action and to place the claims in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call Applicants' attorney, Eric S. Furman, Ph.D., at (619) 687-8643 (direct line) to resolve such issues promptly. Please

charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 10, 2006

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